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Acute renal failure in pregnancy

JEAN-PIERRE GRÜNFELD, DOMINIQUE GANEVAL, and FRANÇOIS BOURNÉRIAS

Clinique Néphrologique, Hôpital Necker, Paris, France

Since the dramatic decrease in the incidence of septic abortion in industrialized countries, acute renal failure (ARF) complicating pregnancy represents a small percentage of the cases of acute renal shutdown, falling in France from 40% in 1966 to 4.5% in 1978 [1]. It is underlined in most series that the mortality rate in ARF associated with pregnancy is lower than that observed in nonobstetric ARF. In their recent survey, Cameron and Brown reported that it ranged from 9 to 34% [2]. This is probably explained by the young age of the patients and, in the most recent studies, also by the earlier detection of the underlying obstetric complications and their better management. Chapman and Legrain indicated that in the Department of Obstetrics at the Foch Hospital in Suresnes, France, no case of acute renal failure was observed among 12,000 delivered women, including 5 with eclampsia and 25 with abruptio placentae [1]. In their large study of 154 women with eclampsia, Pritchard and Pritchard noted only one case of ARF [3].

In contrast with these relatively optimistic data, ARF in pregnancy bears a high risk of bilateral renal cortical necrosis (BRCN), and consequently of chronic renal failure. In 1972, Kleinknecht et al found that the incidence of BRCN was 21% in postpartum renal failure, whereas it was only 1.5% in postabortum ARF. Among 38 cases of BRCN, 26 (68%) were of obstetric origin [4].

In addition to the classical renal complications of pregnancy, idiopathic postpartum ARF has been recognized for the last decade [5]. It often leads to irreversible renal failure and is associated with a high mortality rate. The pathogenesis of this syndrome remains to be elucidated, and its relationship to the idiopathic hemolytic uremic syndrome and thrombotic thrombocytopenic purpura is still debated [5].

The present review is based on the data in the literature and on our own experience with 57 cases of ARF related to pregnancy, referred to the Necker Hospital from 1957 to 1979 (including 47 cases after 1966). Some patients were included in a previous paper from our clinic [4]. Patients with septic abortion were excluded. The main clinical and pathologic features are summarized in Table 1. The circumstances leading to ARF are listed in Table 2. The overall maternal mortality rate was 14% (Table 2).

Acute renal failure due to factors not specific of pregnancy

In our experience this group of patients is characterized by good maternal prognosis because neither maternal death nor BRCN occurred.

Prerenal azotemia secondary to sodium and water loss. Hyperemesis gravidarum and late vomiting of pregnancy may lead to renal disorders, including ARF [6]. This syndrome was often accompanied by kaliopenia resulting in vacuolar renal tubular changes [7]. At present, precise and early correction of water and electrolyte balance should prevent severe renal disturbances.

Acute pyelonephritis and other sepsis. The incidence of acute pyelonephritis is high in pregnancy, occurring in 1 to 2% of all gravidas, and its severity has long been emphasized, even in the most recent studies [8]. The incidence of severe uremia was, however, relatively low. Ober et al, in their survey extending from 1931 to 1954 in Boston, found 8 cases of acute pyelonephritis with uremia leading to death [7]. Hamburger et al at the Necker Hospital observed 2 gravidas with acute pyelonephritis and ARF from 1951 to 1963 [9]. In earlier reports, before the use of antibiotics, severe acute pyelonephritis was occasionally complicated by renal vein thrombosis [10, 11], but this complication did not appear more frequently in pregnant women.

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Septicemia and septic shock are probably the most important pathogenetic factors, and therefore early antibiotic therapy and adequate treatment of shock should prevent this complication. The same holds true in other causes of sepsis in pregnancy.

Occasionally ARF may be related to coincidental factors, for example, drug nephrotoxicity, incompatible blood transfusion, bacterial endocarditis, or acute glomerulonephritis [9, 12, 13].

Acute renal failure due to factors related to and specific of pregnancy

Acute renal failure in eclampsia or severe preeclampsia. Acute renal failure may complicate the course of severe preeclampsia, but its incidence is at present low, probably because of earlier and more appropriate management of preeclampsia and eclampsia [14]. Even in countries where the eclampsia mortality rate remains high, ARF does not develop frequently: Lopez-Llera et al showed that mean plasma creatinine was only slightly elevated in pregnant women who died from eclampsia, and they found evidence of acute tubular necrosis in only 3 women among 33 who underwent autopsy examination [15]. In the studies of ARF in gravidas, however, hypertension or symptoms of preeclampsia were found in a significant proportion of gravidas, for example 62% [16] and 33% [17].

In our studies, severe preeclampsia was present in 12 women, 11 of whom had eclampsia (Table 2). Seizures and hypertension appeared suddenly in 7 patients, and symptoms of toxemia preceded ARF by a few weeks in the 5 other patients. The high percentage of multiparas (10 of 12 patients) should be stressed; the mean age of the patients was 27 yr. Similarly, Kennedy et al indicated that the mean age of their patients with ARF (including postabortum accidents) was 30 yr [17]. In the series of Ober et al [7], there were 5 multiparas among the 13 pregnant women who died from ARF complicating severe preeclampsia. These authors noted a high incidence of arteriolar and arterial renal changes. These data suggest that ARF develops in severe preeclampsia preferentially in older gravidas, who are often multiparas. These cases probably do not represent "true" preeclampsia; they may have undetected chronic hypertension or underlying renal vascular disease, and their remote vascular prognosis is therefore poor [18].

Table 1. Main features in 57 cases of acute renal failure (ARF) in pregnancy

	No. of cases
Parity:	
Nulliparas	16
Multiparas	41
Time of onset:	
Prepartum	8
Pre and postpartum	49[a]
Type of ARF:	
Oligoanuric	41
Polyuric	16
Thrombocytopenia (≤100,000 platelets/mm³)	24
Jaundice (serum total bilirubin ≥ 2.0 mg/dl)	20
Renal pathology:	26[b]
Cortical necrosis	19[c]
Renal thrombotic microangiopathy	4
Glomerular endotheliosis	3
Tubular necrosis	1[d]
Normal kidney	2

[a] Including 5 idiopathic postpartum ARF
[b] 20 biopsies and 6 autopsies
[c] Associated in 2 cases with renal thrombotic microangiopathy
[d] Associated with glomerular endotheliosis

Table 2. Main causes and course of acute renal failure (ARF) in 57 pregnant women

	No. of cases	Age *(mean yr)*	Nulliparas	Time of onset *mean wks*	Fetal death	Maternal death	Cortical necrosis
Acute pyelonephritis	2	21	3	26	0	0	0
Other infections	5	30	3	38	0	0	0
Miscellaneous (unrelated to pregnancy)[a]	7	27	2	34	2	0	0
Severe preeclampsia or eclampsia	12	28	2	35	3	0	1
Abruptio placentae	13	30	1	34	12	2	7
Prolonged intrauterine fetal death	6	32	1	28	6	2	5[b]
Uterine hemorrhage	4	29	1	34	0	0	2
Miscellaneous (related to pregnancy)[c]	2		1		1	2	1
Postpartum idiopathic ARF	5	24	2		0	2	3[b]

[a] Dehydration (2); diabetic ketoacidosis (1); leptospirosis (1); postoperative (1); incompatible blood transfusion (1). The number in parentheses denotes number of cases.
[b] One case was associated with renal thrombotic microangiopathy.
[c] Amniotic fluid embolism (1); late interruption of an ectopic pregnancy (1)

The mechanisms of ARF in preeclampsia are unclear. Swelling of the glomerular endothelial cells is the characteristic renal lesion. It is often stated that the resulting glomerular capillary obstruction leads to postglomerular ischemia and acute tubular necrosis, and eventually to cortical necrosis. Indeed, glomerular endotheliosis was found in almost all cases of eclampsia [15], but there is no evidence that these changes were more severe or diffuse in patients with ARF. Widespread tubular necrosis was frequently reported in autopsy examinations, but Sheehan and Lynch stated that "almost all these reports must be discarded as being based on material from late autopsies" [19]. In their own patients, they found scanty tubular coagulative necrosis in a small number of cases. Minimal unspecific tubular changes were also observed by Ober et al, and tubular necrosis was present in only one fatal case [7]. It should be recalled that the role of tubular necrosis in the pathogenesis of ARF unrelated to nephrotoxins remains to be elucidated [20].

Tubular obstruction has been demonstrated recently in various models of experimental ARF [20, 21] but its contribution to acute pigment nephropathy in the human remains to be proven. Intratubular casts, containing either protein or hemoglobin, were first reported in toxemia of pregnancy at the end of the 19th century (see references in Ref. 22). Approximately 20% of the patients with fatal eclampsia had intratubular hemoglobin casts, suggesting intravascular hemolysis, but the casts were not detected in the initial stage of ARF [22]. Intravascular hemolysis has long been recognized, but it is a rare complication of eclampsia [23]. It may also be hypothesized that some patients with severe generalized convulsions develop myoglobinuria, which may occasionally contribute to ARF.

Brain, Kuah, and Dixon [24] considered intravascular hemolysis occurring in eclamptic women as evidence of intravascular coagulation. Fragmented and distorted red blood cells were found, indicating microangiopathic hemolytic anemia (MHA). These authors suggested the hypothesis that erythrocytes were damaged in the initial phase of fibrin deposition and microthrombus formation. Platelets were similarly altered, then removed from circulation at the site of thrombus formation or by the reticuloendothelial system, accounting for thrombopenia. A similar sequence of events could be involved in various clinical conditions, such as severe preeclampsia or eclampsia, hemolytic uremic syndrome, or malignant hypertension. In their review, Brain et al collected 14 previously reported cases (involving 7 nulliparas); all affected women had raised blood urea and the onset of MHA always preceded the appearance of uremia; the maternal mortality rate was 64% [24]. Disseminated vascular lesions with arteriolar fibrinoid necrosis and intimal proliferation were documented in some patients. Focal renal cortical necrosis was found in 4 patients. The authors suggested that heparin might be of value in the treatment of this syndrome, but in the case they reported, a first episode during a previous pregnancy had remitted spontaneously [24]. Sheehan and Lynch pointed out, however, that hemoglobin casts resulting from hemolysis and hemoglobinuria were not often encountered in endotoxin shock, where diffuse thrombi were commonly found. In contrast, disseminated intravascular thrombi were not found in eclampsia [25]. This question will be discussed below.

Abruptio placentae and other complications of pregnancy. In our studies (Table 2), approximately 50% (7/13) of the gravidas with ARF complicating abruptio placentae had bilateral renal cortical necrosis (BRCN). Fifty percent of the fatal cases of abruptio placentae were associated with BRCN in another study [26]. Other complications of pregnancy, such as prolonged intrauterine fetal death or amniotic fluid embolism, may induce ARF [12]. All these complications are accompanied by coagulation defects, including low plasma fibrinogen levels [27].

Uterine hemorrhage. Hemorrhage and hypotension were implicated as major etiologic factors in 7% of our patients (Table 2) and in 16% in the series of Kennedy et al [17]. They were precipitating factors in 58% in the study of Smith et al [16]. The importance of bleeding may be underestimated if it is not externally obvious. Early and adequate (usually large) blood transfusion is the best means of preventing renal functional shutdown [16].

Hypervolemia should protect the parturient against the effects of blood loss, which may be substantial even during and after a relatively normal delivery. It has been suggested that renal function in toxemic women is highly sensitive to blood loss. For example, Smith et al noted that among 18 toxemic women, ARF seemed to be precipitated by hemorrhage in 11 [16]. Various mechanisms may explain this hypersensitivity. Preeclamptic women have lower plasma volume and renal blood flow, and higher pressor responsiveness to norepinephrine and angiotensin II than do normotensive gravidas. It has been shown that placentae of preeclamptic patients release less prostaglandin than

do those of normal gravidas, and relative prostaglandin deficiency may be involved in the hypersensitivity to hemorrhage [28]. Last, coagulation changes observed in pregnancy (see below) may facilitate the development of ARF. It is worth noting that none of our 4 patients with hemorrhage and ARF were toxemic. Two of them developed BRCN, which would appear to be a high incidence. In the study of Smith et al [16], hypertension and bleeding were frequently associated in women with BRCN, but in their case 7, antepartum hemorrhage in the absence of preeclampsia was the only triggering factor detected.

Bilateral renal cortical necrosis

It is clear that pregnant women with ARF are at high risk of BRCN. In the studies of Smith et al, 8 cases of BRCN (27%) were recognized; all affected women died [16]. In India, BRCN was present in 37.8% of the women with ARF in late pregnancy [29]. In our study, the incidence was 33%; one patient developed panhypopituitarism, which was probably related to concomitant pituitary necrosis, and necessitated continuous hormonal therapy. Patchy cortical necrosis with partial or nearly complete recovery of renal function may be overlooked in surviving patients if adequate investigations are not performed. The real incidence of BRCN may therefore be underestimated in the studies where only autopsy data were available.

Bilateral cortical necrosis tends to occur more often in certain obstetric complications. The incidence is high in abruptio placentae (see above). Eighty percent of fatal BRCN were associated with uteroplacental apoplexy in the Boston study [7]. In our studies, prolonged intrauterine fetal death also carries a high risk of BRCN, because this complication was documented in 5 of 6 cases (Table 2). In contrast, the incidence is relatively low in severe preeclampsia (Table 2). Sheehan and Lynch indicated that it was noted in only 2% of gravidas with fatal preeclampsia [26].

Ober et al found that BRCN occurred mainly in pregnant women over 30 yrs of age with coexistent nephrosclerotic changes [7], but it may develop in younger subjects, as shown in previous studies [4, 16] and in our present study in which 5 patients were under 25 yr of age. It is generally accepted that toxemic symptoms often, but not invariably [16] precede BRCN. Kleinknecht et al, however, noted that toxemic symptoms were less common in patients with BRCN than they were in those with reversible ARF and full recovery. In addition, they showed that in women with BRCN, acute renal failure appeared earlier in gestation [4]. The analysis of the present series confirmed our previous findings [4], but the early occurrence of BRCN was mainly due to the early ARF in women with prolonged intrauterine fetal death in whom BRCN was almost a constant occurrence (Table 2). Data from patients with ARF and abruptio placentae are analyzed in Table 3. There is no striking difference between the two groups, except that polyuric ARF was not observed in BRCN; women with BRCN were not older than those with full recovery. It is difficult to assess the true incidence of toxemia in patients with abruptio placentae because many are emergency admissions, and a normal or low blood pressure at that time does not exclude a previous short toxemic period.

The diagnosis of BRCN should be suspected in a pregnant woman, particularly when ARF develops before the 30th week of gestation, even in the absence of toxemic symptoms, and when the oliguric or anuric stage is prolonged beyond 10 days [4]. The positive diagnosis is based on renal biopsy and/or selective arteriography data [4]. These two methods may provide information on the extent of the cortical necrosis [4], differentiating extensive BRCN characterized by a large percentage of destroyed

Table 3. Cases of abruptio placentae with acute renal failure (ARF)

	Reversible ARF with full recovery ($N = 6$)	Bilateral renal cortical necrosis ($N = 7$)
Age, *yr*	29.2 ± 1.8[a]	30.4 ± 1.8[a]
Time of gestation, *wks*	32.8 ± 1.5[a]	34.3 ± 1.8[a]
Nullipara	1	0
Toxemia	2	2
Polyuric ARF	4	0
Epsilon aminocaproic acid administration	3	5
Thrombocytes, $\times 10^3$, *per* mm^3	138 ± 28[a]	65 ± 26[a, b]

[a] Values are the means ± SEM.
[b] $N = 6$; $t = 1.93$, $P > 0.05$, NS (Student's t test)

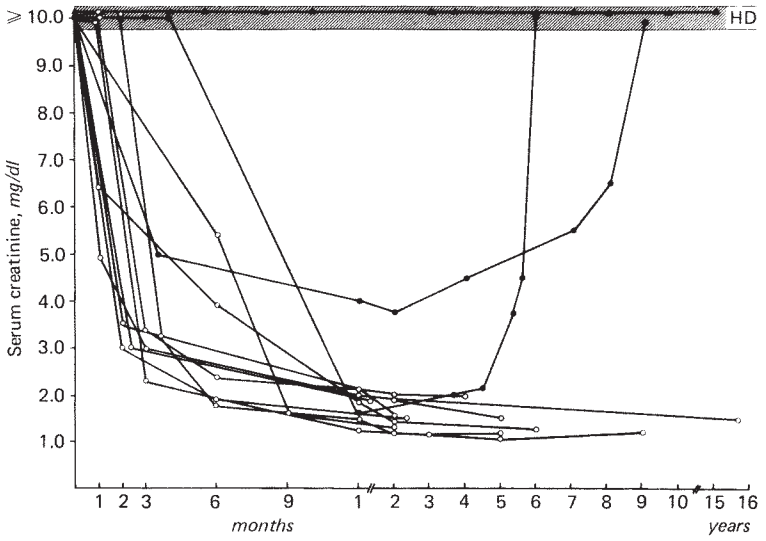

Fig. 1. *Outcome of 13 patients with obstetric bilateral renal cortical necrosis.* HD is hemodialysis.

glomeruli, and the lack of cortical nephrogram, from patchy cortical necrosis where a larger percentage of glomeruli are spared and the cortical nephrogram is striated and heterogeneous. Cortical calcifications may be seen on X-rays after a few weeks [4, 26].

It is well recognized that patients with BRCN may slowly recover renal function [30]. Renal function may improve until the third year after the onset [4, 31]. In the patient described by Effersoe Raaschou, and Thomsen, BRCN was followed by two uneventful pregnancies [31]. In most patients who survived the acute phase of ARF, residual renal function resumed (Fig. 1). Permanent hemodialysis was required after the acute phase in only one patient. Chronic dialysis may occasionally be temporarily discontinued. Such a course is illustrated in Fig. 1: in two patients hemodialysis was performed for 1 and 4 months, then interrupted for 5 and 9 yr, respectively, because renal function improved and stabilized. Unfortunately, it subsequently deteriorated and maintenance hemodialysis had to be again instituted. Successful renal transplantation has been reported [4], but some authors have pointed out the high risk of acute rejection in patients with previous BRCN [32].

Acute renal failure in acute fatty liver of pregnancy

Acute fatty liver is a rare complication of pregnancy; approximately 60 cases have been reported so far [33–35].

Typically the first manifestations (fever, nausea, vomiting, and abdominal pain) appear in the prepartum or in the early postpartum period, less often in the third trimester of pregnancy. They are rapidly accompanied by jaundice, which is characterized by normal serum alkaline phosphatase, minimal increase in serum transaminase, and, occasionally, increased serum amylase activities [35]. Toxemia was reported in about 20% of the cases [35]. Pathologic liver changes are characterized by microvacuolar fatty infiltration with centrilobular dominance. There is no loss of lobular structure, and no significant necrosis or cellular infiltrate. Fatty liver of pregnancy has been reported following tetracycline or related antibiotic compound therapy [36].

The incidence of ARF in this condition is high, reaching 60% or more [33, 35]. The mortality rate is as high as 70 to 75% for both the fetus and the mother [33, 35], but it appears to be primarily the result of hepatic rather than renal failure. ARF may occur either early or late in the preterminal course. The prognosis has improved in the patients treated since 1970 [37–39].

Various, and often slight, renal histopathologic changes have been described. Kidney structure may be within normal limits [35, 40]. Fine fatty vacuolization of the tubular cells was noted in several cases. These lesions may be slight and were found in patients with normal renal function [41]. Focal tubular necrosis or nonspecific changes consistent with tubular regeneration were also detected [42]. Occasionally, glomerular lesions were observed: intraglomerular thrombi [43] suggesting intravascular coagulation, or membranoproliferative changes [44]. Morrin et al [45] described, by light and elec-

tron microscopy, segmental occlusions of capillary lumina by fibrin-like material in about 50% of the glomeruli; the subendothelial spaces were prominent and appeared to be occupied by a fibrillar material. These changes resemble those reported in toxemia or in the hemolytic uremic syndrome [45]. It should be noted that there was no pathologic evidence of acute fatty liver in the case studied by Morrin et al because liver biopsy was normal but was performed late in the course [45]. This emphasizes the need of adequate kidney and liver biopsy data in this syndrome. Jaundice is frequently found in ARF from other causes in pregnancy: of the 57 patients in our study, 20 had jaundice (Table 1). The diagnosis of fatty liver should therefore be based on unquestionable pathologic findings.

The pathogenesis of ARF in acute yellow atrophy of liver in pregnancy is unknown. Shock is not a constant finding. Acute pancreatitis was possibly a precipitating factor in some cases [35]. Abnormalities suggestive of disseminated intravascular coagulation have been detected in patients investigated since 1970 [35, 38, 40]. Intraglomerular deposition of fibrin has been demonstrated in some patients [38, 45], but no case of BRCN has so far been reported. Fatty liver of pregnancy shows some similarities with Reye's syndrome, or fatty change with encephalopathy, observed in children. In this syndrome, serum transaminase activities are increased, and central nervous system disturbances are prominent. In addition, ARF is rare in Reye's syndrome, although the kidney shows fatty changes [46]. In contrast, renal failure has been more frequently noted in children with encephalopathy and hepatic dysfunction, a syndrome differing from Reye's syndrome by the absence of diagnostic liver changes [47]. Finally, many features of ARF in fatty liver resemble the so-called "hepatorenal syndrome" reported in various hepatic disorders, in which hemodynamic factors are probably prominent.

Idiopathic postpartum acute renal failure

The first cases of idiopathic postpartum ARF were published during 1966 to 1968 under various labels [12, 26], but occasional cases had possibly been reported previously (see references in Ref. 26, and case 8 in Ref. 16). It is not clear whether this entity was misdiagnosed in the past or is a new disease [26]. Recent drugs used at delivery, such as ergot alkaloids, were incriminated in its causation, but without conclusive evidence. Thirty cases were reviewed in 1976 by Schoolwerth et al [5]. Twenty-one additional cases were found in the literature [26, 48–59].[1]

Typically, the syndrome begins 1 day to several weeks postpartum. The term "late puerperal renal failure" is therefore inappropriate [26]. The pregnancy had usually been uneventful, without hypertension, in a previously healthy woman. In many patients the initial symptoms simulated a flu-like syndrome. Subsequently, severe, often anuric, ARF developed rapidly. Initially, the blood pressure was usually normal or slightly elevated, but in many cases hypertension appeared later in the course. Microangiopathic hemolytic anemia (that is, anemia, numerous schistocytes, high reticulocyte count, and low serum haptoglobin level) was documented in many patients, but not in all [5]. The term "postpartum hemolytic uremic syndrome" is therefore appropriate only in cases with MHA. Thrombocytopenia was found less frequently. Two thirds of the patients died or required chronic dialysis, but a few women had recovery of renal function [5].

Besides the idiopathic postpartum ARF as defined above, many atypical cases are described under the same term, and therefore evaluation of the therapy used is difficult or impossible.

(1) Time of onset. In most instances, ARF occurs either early, within a few days, or slightly later, within a few weeks, postpartum [5]. In our study (Table 2), ARF developed within 1 day postpartum in two women, after a normal pregnancy; both had cortical necrosis (see also cases 6 and 8 in Ref. 16). In the three others, renal failure appeared later and renal thrombotic microangiopathy was found on the biopsy specimen.

In a few women [51, 60], the syndrome began during pregnancy. At the other extreme, in several other patients it occurred at 5 [60], 6, and 7.5 months postpartum [61]. It is unknown whether in the latter cases pregnancy was involved. Recurrent postpartum hemolytic uremic syndrome (HUS) has been reported [57]. Similarly, severe preeclampsia with MHA and ARF may recur in subsequent pregnancies [24].

[1]Since the submission of the manuscript, three additional cases of postpartum hemolytic uremic syndrome were reported by Segonds et al (*Clin Nephrol* 12:229–242, 1979). The authors emphasize the possible occurrence of slight hypocomplementemia, an abnormality already observed in some patients with HUS. On the other hand, Hensby et al (*Lancet* 2:748, 1979) found a deficiency in prostacyclin production and a platelet unresponsiveness to exogenous prostacyclin in a 45-yr-old female patient with severe PTT. Prostaglandin metabolism requires further study in postpartum HUS.

(2) Hypertension. Hypertension or toxemia preceded postpartum ARF in several cases [48, 52, 54, 55, 60, 62]. We pointed out above that severe preeclampsia may include MHA [24]. Thus, it may be difficult to differentiate on clinical grounds severe preeclampsia with renal failure and MHA from idiopathic postpartum ARF. In addition, eclampsia may suddenly appear within 48 hr postpartum, and may be complicated with ARF.

In some reports, severe hypertension was noted initially in the course of postpartum ARF [48, 51, 55, 58, 60]. In these cases, the possibility of malignant nephrosclerosis might be considered, because malignant hypertension in nonpregnant subjects may be accompanied by MHA and uremia.

(3) Extrarenal involvement. Thrombotic thrombocytopenic purpura (TTP) may develop during pregnancy [26, 63, 64] or even in the postpartum period [65, 66], and renal function may be impaired. Idiopathic postpartum ARF may mimic TTP because multisystem [48] or, more often, central nervous system involvement (leading to lethargy, coma, or grand mal seizures) [51, 57, 62] have been described. The high incidence of cardiac failure was stressed by Robson et al [67]. As in TTP, autopsy revealed disseminated thrombi in the case studied by Rosenmann et al. In this case, fatty liver of pregnancy was also found and was possibly related to tetracycline therapy [62]. Extrarenal foci of arteriolar necrosis were also found by Churg et al [61].

(4) Renal pathology. Histopathologic findings are heterogeneous. Scattered areas of cortical necrosis may be found. Some pathologists have stressed the importance of the arterial/arteriolar changes suggestive of nephrosclerosis (hence the term "postpartum nephrosclerosis") [5], whereas others [67] pointed out the peculiar lesions suggestive of thrombotic microangiopathy, involving glomerular capillaries and arterioles, as described by Symmers in 1952. The latter type of lesions is well illustrated by the case reported by Rosenmann et al: the glomerular endothelial cells were enlarged; fibrin thrombi were found in many afferent arterioles and glomeruli; obstruction of glomerular capillaries resulted from endothelial swelling and large subendothelial deposits which were granular and enmeshed with strands of fibrillar material with the characteristic periodicity of fibrin; identical deposits were detected in afferent arterioles; and last, there was increased prominence of the mesangial areas [62]. These changes are similar to those found in the hemolytic uremic syndrome in young children [68]. On the other hand, vascular lesions characteristic of malignant nephrosclerosis (or of kidney involvement in scleroderma with ARF) were also often described [5, 52]. Glomeruli were ischemic with wrinkled basement membranes; when glomerular necrosis was present, it was considered to be the extension of the arteriolar fibrinoid necrosis. The vascular lesions also involved the intralobular arteries.

So far, it is unclear whether these two types of lesions correspond to different entities or whether they represent successive stages of the same disease. The time of the renal biopsy may be critical, but the data available in the literature do not provide definite information in this regard [50]. In our experience, the renal lesions found in idiopathic HUS in adults whose blood pressure was initially normal or slightly increased [68] diffusely involved arterioles and intralobular arteries in nearly all cases. The glomerular changes, however, were of either type—that is, microangiopathic (Fig. 2) as in children, or ischemic (Fig. 3)—even early in the course of the disease; the mean age of the patients with ischemic changes was higher. When late anatomical data were obtained from patients with irreversible renal failure, microangiopathic glomerular lesions could still be present; but in most cases, changes suggestive of glomerular ischemia were found as in nephrosclerosis (D. Droz, D. Ganeval, and R. Habib, unpublished results). Among the four cases of renal thrombotic microangiopathy included in the present study, one was complicated by prolonged intrauterine fetal death; the 3 others occurred in the postpartum period; in all, glomerular changes were prominently ischemic.

Heptinstall pointed out that the degree of vascular involvement was of predictive value in the hemolytic-uremic syndrome [70]. Recently, Morel-Maroger et al showed that the degree of arterial intimal thickening was significantly less severe in adult patients with hemolytic-uremic syndrome and relatively good outcome than it was in those with poor outcome, whereas there was no difference in the overall severity of the glomerular changes between the two groups [58]. They included in their study, however, many patients who initially were severely hypertensive.

Immunofluorescent study usually revealed fibrin and occasionally β_1C globulin in glomeruli and arterioles [5, 52, 58]. Focal staining with anti-IgG and IgM antisera was found in some patients [5], but glomeruli generally did not stain, except in minute amounts in rare cases [61, 62].

A relatively high incidence of severe postbiopsy

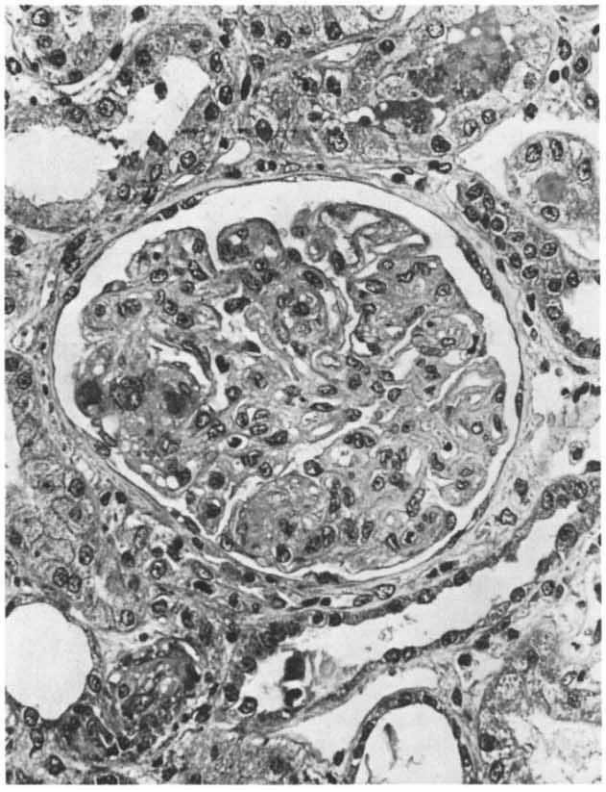

Fig. 2. *Glomerular involvement of microangiopathic type in a woman with postpill HUS.* The tuft is enlarged. Glomerular capillary walls are strikingly thickened with "double contour," and fibrin thrombi are present in some capillary lumina. Note thrombus in the juxtaglomerular arteriole. (×450; courtesy of Dr. D. Droz).

Fig. 3. *Glomerular ischemic changes in a woman with idiopathic postpartum HUS.* The glomerulus shows ischemic changes with diffuse wrinkling of the glomerular basement membranes. (×450; courtesy of Dr. D. Droz).

hemorrhage was reported [58], especially when heparin therapy was instituted a few days after renal biopsy [58], but also in hypertensive patients who did not receive heparin [60, 61]. The indication for renal biopsy should be carefully discussed in each case, with regard to its value for diagnosis and therapeutical decision. Renal biopsy is undoubtedly necessary in patients who do not have MHA. In contrast, in patients with unequivocal HUS, the clinical usefulness of renal biopsy may be questioned (see below).

(5) Oral contraceptives. Tobon [71], then Brown et al [71] first described the occurrence of the hemolytic-uremic syndrome in women taking oral contraceptives. Severe hypertension is often present [70], but the syndrome may develop in women with normal blood pressure [5, 71]. Among those with late postpartum ARF, some were taking contraceptives [50, 58, 61, 73]. It is not clear whether in these cases the HUS should be ascribed to pregnancy or to the oral contraceptive agents.

Renal histopathologic changes in postpill hemolytic-uremic syndrome were succinctly described [72]. Renal changes were considered compatible with malignant nephrosclerosis [5] or with thrombotic microangiopathy [71]. We observed 5 women with this syndrome (D. Ganeval and D. Droz, unpublished data); 3 died and the other 2 required periodic maintenance hemodialysis. Renal biopsy was performed in all; in 4 of them it showed changes of glomerular capillaries resembling those found in the HUS in young children (Fig. 2), but arteriolar lesions were more diffuse.

There is no good evidence that postpill and postpartum renal failure share similar pathogenetic mechanism(s). Cases were reported in which hypertension and severe renal failure followed oral contraceptive administration, whereas pregnancies had been uneventful in these women [74, 75]. Pritchard and Pritchard noted a similar dissociation between pregnancy-induced hypertension and postpill hypertension [76]. A genetic predisposition may also be involved: hemolytic-uremic syndrome [77] and TTP [78] have been reported in siblings taking oral

contraceptives. In two sisters, TTP occurred during late pregnancy, 2 years apart [64]. The familial occurrence of hemolytic-uremic syndrome has been emphasized repeatedly [79]. In the unique kindred described by Grøttum et al as "immunological hereditary nephropathy" with MHA, 3 women developed progressive renal failure during pregnancy [80].

(6) Therapy. Is heparin therapy beneficial in the management of postpartum ARF? From the review of Schoolwerth et al [5] and from subsequent data, it is apparent that heparin failed to improve renal function in many patients [49, 51, 55, 56]. Most "positive" reports contain one single successful case [5, 52], and "negative" results have probably not been published. Only one paper [60] includes 5 patients; they were treated by several drugs, including heparin; only one death occurred, the 4 other women recovered renal function. The cases reported were quite uncommon, however: 4 of the patients had toxemic symptoms and were severely hypertensive in the early stage of ARF; in 3, severe uterine and/or postrenal biopsy hemorrhage was noted and may have contributed to the severity of ARF [60]. It is therefore difficult to evaluate the beneficial effect of heparin. It should also be recalled that there is no evidence that heparin therapy is beneficial in the hemolytic-uremic syndrome in children [81].

Morel-Maroger et al proposed more vigorous heparin therapy in patients with less severe vascular lesions because, in their studies, these patients had a better prospect of renal recovery [58]. Their study contains no evidence that heparin therapy was beneficial in the 4 patients with postpartum HUS: all 4 were treated, with success in only 2 [58]. In late cases, with extensive and irreversible vascular changes, renal biopsy was considered dangerous, and anticoagulation unwarranted [58]. In our study, none of the 4 patients with HUS and renal thrombotic microangiopathy was treated with heparin, yet 2 had a good outcome with complete or partial recovery.

Thus, it may be reasonably questioned whether heparin is of value in postpartum ARF and whether conservative management, including dialysis and antihypertensive drugs when necessary, is not a better choice. The latter therapeutic approach is reasonable in hypertensive patients with severe vascular changes in the renal biopsy specimen. In contrast, in women with ARF and unequivocal MHA, in the absence of severe hypertension, heparin therapy may be contemplated. Two possibilities are open: either to perform renal biopsy to evaluate whether or not heparin therapy is indicated (the risk of renal bleeding from the biopsy site during heparin therapy has to be considered), or to institute rapidly heparin therapy without renal biopsy (with the risk of including unproven cases).

Fibrinolytic therapy has also been tried, without significant effect on renal function (see Eisenger in Refs. 5, 56). The therapeutic approaches attempted in TTP may be aplied to postpartum HUS. Administration of antiplatelet agents was advocated in TTP [82]. Thus, Thorsen et al found a beneficial effect of dipyridamole and aspirin in 2 cases of "hemolytic uremic syndrome"; however, one of them had no renal failure. Both patients had severe preeclampsia, possibly responsible for the hematologic changes, and spontaneous recovery could have been expected after delivery [83]. Plasmapheresis or rather plasma infusion, was recently advocated. In a woman with TTP appearing during pregnancy, plasma infusion had a beneficial effect on the hematologic and renal abnormalities [84].

Bilateral nephrectomy was performed in some patients [5, 50, 58]. MHA may clear following nephrectomy, as it may occur in idiopathic HUS. Nephrectomy is highly valuable in women with progressively intractable hypertension [59], but it should be reserved for these patients, because renal function has recovered partially in occasional cases after a long period of dialysis, as in idiopathic HUS and other vascular renal diseases [86]. Successful renal transplantation was performed in patients with postpartum ARF without recurrence of the disease [50, 55, 58] (2 cases in the present series).

Role of intravascular coagulation in acute renal failure during pregnancy and the postpartum period

Normal pregnancy is accompanied by an enhanced capacity to produce fibrin (increased levels of plasma fibrinogen, and of factors VII, VIII, and X), whereas removal activity is depressed. The decreased fibrinolytic activity returns to normal within 0.5 to 1.0 hour after placental delivery. In preeclampsia, a reduced number of circulating platelets, increased levels of serum fibrin degradation products (FDP), and enhanced thrombin activity are commonly found. In addition, fibrinolytic activity returns to normal several days after placental delivery [86]. Intravascular fibrin deposition was found in renal glomeruli of preeclamptic women (at least in severe forms). In abruptio placentae and prolonged intrauterine fetal death, the fibrinogen concentration at term was below the normal value,

factors V and VIII levels were markedly reduced, and FDP levels were elevated but no evidence of systemic fibrinolysis was observed [27]. Similarly, severe postpartum hemorrhage and amniotic fluid embolism may also lead to the defibrination syndrome [27]. The release of thromboplastin from a placental or amniotic site has been proposed as the triggering factor of these clotting disorders.

The coagulation disturbances observed in normal gestation and especially in complicated pregnancy have led to the hypothesis that these disorders may facilitate the development of obstetric ARF. The high incidence of BRCN further suggested that intravascular coagulation phenomena are involved in the pathogenesis of obstetric ARF. The consequences of intravascular coagulation and its extent (from localized to disseminated changes) depend on several factors: the triggering event, the duration and severity of the clotting disturbances, the presence or absence of endothelial damage, the rate of organ blood flow, and the rate of clearing of the various activated components of the clotting system. This might explain the wide clinical spectrum of renal changes found in pregnancy, from glomerular endotheliosis to BRCN and postpartum ARF.

This unifying concept is further supported by experimental and pathologic data. It has been stated repeatedly that eclampsia, BRCN, and other acute fatal complications of pregnancy represented the clinical counterpart of the experimental Shwartzman reaction in which bilateral renal cortical necrosis is the main feature [87]. In contrast to nonpregnant animals, only one injection of endotoxin was required to elicit the generalized reaction in pregnant rabbits. Kincaid-Smith concluded from her pathologic studies that similar primary renal lesions were found and a similar pathogenetic mechanism was involved in preeclampsia, postpartum benign ARF, and postpartum irreversible ARF, the only difference being in the extent and severity of the pathologic changes [88].

In contrast, it should be recalled that clinical data do not convincingly demonstrate the primary role of disordered coagulation in obstetric ARF. There is no evidence that in preeclampsia, abruptio placentae, or prolonged intrauterine fetal death, coagulation abnormalities are more severe in women with ARF than in those without it. The severity of ARF is not closely related to the intensity of coagulation disturbances. In patients with postpartum ARF, clotting studies were often incomplete, but data consistent with intravascular coagulation were scarce, whereas renal failure was frequently irreversible [5]. In obstetric patients, Chugh et al found that disseminated intravascular coagulation (DIC) was seen more frequently in cases of acute tubular necrosis than in cortical necrosis [29]. The incidence of BRCN in obstetric patients with ARF (including early postabortum) was identical in women with and without DIC [89]. Some results suggest, however, that coagulation phenomena may contribute to cortical necrosis. Gravidas with BRCN had a significantly lower plasma fibrinogen and slightly lower thrombocyte count than did pregnant women with ARF who recovered fully [4]. In the short series of women with abruptio placentae, we confirmed that platelet counts were lower (but not significantly so) in those with BRCN (Table 3). Wardle showed that experimental placental abruption in the rabbit was followed by a defibrination syndrome, but that renal cortical necrosis only resulted when fibrinolysis was further inhibited by epsilon-aminocaproic acid [90]. In this regard, it is worth noting that this drug, with or without fibrinogen infusion, had been administered to 10 of our patients who subsequently developed BRCN. In the group with abruptio placentae, however, the administration of the drug was not significantly more frequent in gravidas with BRCN (Table 3).

The use of heparin is still controversial, and there is no evidence that this drug has a preventive effect in pregnant women at high risk of ARF. Pritchard et al used magnesium sulfate, antihypertensive drugs, and adequate obstetric management in the treatment of eclamptic women, mainly primiparas. No maternal death occurred, and only one case of ARF was reported among 161 patients [3, 14]. These authors do not therefore advocate heparin therapy [91]. The usefulness of heparin may be questioned in preeclamptic multiparas in whom chronic vascular renal disease is often present and in whom severe ARF with BRCN might be more frequent. Obvious dangers, however, outweigh any theoretic and unproven benefits. The use of heparin should also be viewed with caution in abruptio placentae and in prolonged intrauterine fetal death. In some cases of defibrination, it may aggravate the condition or cause severe hemorrhage from the uterus or in the central nervous system if high blood pressure is present [27].

It is still unclear whether coagulation changes represent the primary event in ARF related to some complications of pregnancy. Some authors [23, 25] stressed the primacy of vasospasm in preeclampsia and of endothelial lesions in postpartum ARF. A striking feature in BRCN was the absence of renal thrombi in specimens obtained early in the course, whereas late specimens contained thrombi [25]. Endothelial damage or disruption probably initiated

platelet adherence and fibrin deposition [23, 25], phenomena which may play an aggravating role in tissue ischemia. The data of Raij, Keane, and Michael may be relevant in this regard. These authors induced unilateral renal Shwartzman reaction and showed that the initial event in the genesis of cortical necrosis was a specific local effect of endotoxin on the vascular endothelium [92]. These data support previous results suggesting that thrombi form in situ in areas of endothelial damage.

Dialysis in obstetric ARF

Both peritoneal dialysis and hemodialysis have been used in gravidas with ARF. Many prefer peritoneal dialysis or consider the procedure safe provided "the catheter is inserted high in the abdomen under direct vision through a small incision" [93]. During hemodialysis, anticoagulation and fluid balance should be carefully monitored. Forty-two patients in our study were treated by hemodialysis, but none before delivery.

In some cases, the onset of ARF preceded the delivery of a live infant [6, 94]. If the conceptus is mature, it should be delivered as soon as the mother's condition has been stabilized [93]. It is often stated that the prognosis for the fetus is worse than that for the mother with ARF [93]. In our study, the 8 cases of prepartum ARF were associated with 2 fetal deaths and no maternal death.

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Reprint requests to Dr. J. P. Grünfeld, Clinique Néphrologique, Hôpital Necker, 161 rue de Sèvres, 75730 Paris, Cedex 15, France

References

1. Chapman A, Legrain M: Acute tubular necrosis and interstitial nephritis, in *Nephrology*, edited by Hamburger J, Crosnier J, Grünfeld JP, New York, John Wiley and Sons, 1979, p. 383
2. Cameron JS, Brown CB: The investigation and management of acute uremia, in *Nephrology*, edited by Hamburger J, Crosnier J, Grünfeld JP, New York, John Wiley and Sons, 1979, p. 255
3. Pritchard JA, Pritchard SA: Standardized treatment of 154 cases of eclampsia. *Am J Obstet Gynecol* 123:543–552, 1975
4. Kleinknecht D, Grünfeld JP, Cia Gomez P, Moreau JF, Garcia-Torres R: Diagnostic procedures and long-term prognosis in bilateral renal cortical necrosis. *Kidney Int* 4:390–400, 1973
5. Schoolwerth AC, Sandler RS, Klahr S, Kissane JM: Nephrosclerosis postpartum and in women taking oral contraceptives. *Arch Intern Med* 136:178–185, 1976
6. Soyannowo Mao, Armstrong MJ, McGeown MG: Survival of a foetus in a patient with acute renal failure. *Lancet* 2:1009–1011, 1966
7. Ober WE, Reid DE, Romney SL, Merrill JP: Renal lesions and acute renal failure in pregnancy. *Am J Med* 21:781–810, 1956
8. Cunningham FG, Morris GB, Mickal A: Acute pyelonephritis of pregnancy: A clinical review. *Obstet Gynecol* 42:112–117, 1973
9. Hamburger J, Richet G, Crosnier J, Funck-Brentano JL, Antoine B, Ducrot H, Mery JP, De Montera H: *Nephrology*. Philadelphia, W. B. Saunders Company, 1968, p. 1312
10. Richet G, Meyrier A: *Liposclérose Rétropéritonéale: Thrombose des Veines Rénales. Deux Syndromes Rétropéritonéaux*. Paris, Masson, 1970, p. 179
11. Sheehan HL, Lynch JB: *Pathology of Toxaemia of Pregnancy*. Edinburgh and London, Churchill Livingstone, 1973, p. 300
12. Lindheimer MD, Katz AI: *Kidney Function and Disease in Pregnancy*. Philadelphia, Lea and Febiger, 1977, p. 119
13. Sheehan HL, Lynch JB: *Pathology of Toxaemia of Pregnancy*. Edinburgh and London, Churchill Livingstone, 1973, p. 302
14. Pritchard JA: Management of severe preeclampsia and eclampsia. *Semin Perinat* 2:83–97, 1978
15. Lopez-Llera M, Linares GR: Factors that influence maternal mortality in eclampsia, in *Hypertension in Pregnancy*, edited by Lindheimer MD, Katz AI, Zuspan FP, New York, John Wiley and Sons, 1976, p. 41
16. Smith K, Browne JCM, Schackman R, Wrong OM: Acute renal failure of obstetric origin: An analysis of 70 patients. *Lancet* 2:351–354, 1965
17. Kennedy AC, Burton JA, Luke RG, Briggs JD, Linsay RM, Allison MEM, Edward N, Dargie HJ: Factors affecting the prognosis in acute renal failure. *Quart J Med* 42:73–86, 1973
18. Chesley LC, Annitto JE, Cosgrove RA: The remote prognosis of eclamptic women. *Am J Obstet Gynecol* 124:446–459, 1976
19. Sheehan HL, Lynch JB: *Pathology of Toxaemia of Pregnancy*. Edinburgh and London, Churchill Livingstone, 1973, p. 194
20. Stein JH, Lifschitz MD, Barnes LD: Current concepts on the pathophysiology of acute renal failure. *Am J Physiol* 234(3):F171–F181, 1978
21. Mason J, Olbricht C, Takabatake T, Thurau K: The early phase of experimental acute renal failure: I. Intratubular pressure and obstruction. *Pfluegers Arch* 370:155–163, 1977
22. Sheehan HL, Lynch JB: *Pathology of Toxaemia of Pregnancy*. Edinburgh and London, Churchill Livingstone, 1973, p. 220
23. Cunningham FG, Pritchard JA: Hematologic considerations of pregnancy-induced hypertension. *Semin Perinat* 2:29–38, 1978
24. Brain MC, Kuah KB, Dixon HG: Heparin treatment of haemolysis and thrombocytopenia in pre-eclampsia. *J Obstet Gynaecol Br Cwlth* 74:702–711, 1967
25. Sheehan HL, Lynch JB: *Pathology of Toxaemia of Pregnancy*. Edinburgh and London, Churchill Livingstone, 1973, p. 686
26. Sheehan HL, Lynch JB: *Pathology of Toxaemia of Pregnancy*. Edinburgh and London, Churchill Livingstone, 1973, p. 287
27. Kleiner GJ, Greston WM: Current concepts of defibrina-

tion in the pregnant woman. *J Reprod Med* 17:309–317, 1976
28. Henrich L, Anderson RJ, Berns AS, McDonald KM, Pauben PJ, Berl T, Schrier RW: The role of renal nerves and prostaglandins in control of renal hemodynamics and plasma renin activity during hypotensive hemorrhage in the dogs. *J Clin Invest* 61:744–750, 1978
29. Chugh KS, Singhal PC, Sharma BK, Pal Y, Mathew MT, Dhall K, Datta BN: Acute renal failure of obstetric origin. *Obstet Gynecol* 48:642–646, 1976
30. Riff DP, Wilson DM, Dunea G, Schwartz FD, Kark RM: Renocortical necrosis. Partial recovery after 49 days of oliguria. *Arch Intern Med* 119:518–521, 1967
31. Effersoe P, Raaschou F, Thomsen AC: Bilateral renal cortical necrosis: A patient follow-up over 8 years. *Am J Med* 33:455–458, 1962
32. Gelfand MC, Friedman EA, Knepshield JH, Karpatkin S: Detection of antiplatelet antibody in patients with renal cortical necrosis. *Kidney Int* 6:426–430, 1974
33. Nash DT, Tomaszewicz T: Acute yellow atrophy of liver in pregnancy. *NY State J Med* 71:458–465, 1971
34. Holzbach RT: Jaundice in pregnancy—1976. *Am J Med* 61:367–376, 1976
35. Blétry O, Roche-Sicot J, Rueff B, Degott C: Stéatose hépatique aiguë gravidique. *Nouv Presse Méd* 8:1835–1838, 1979
36. Kunelis CT, Peters TL, Edmondson HA: Fatty liver of pregnancy and its relationship to tetracycline therapy. *Am J Med* 38:359–377, 1965
37. Breen KJ, Perkins KW, Mistilis SP, Shearman R: Idiopathic acute fatty liver of pregnancy. *Gut* 11:822–825, 1970
38. Holzbach RT: Acute fatty liver of pregnancy with disseminated intravascular coagulation. *Obstet Gynecol* 43:740–744, 1974
39. McKenna J, Pupkin M, Crewshaw C, McLeod M, Parker RT: Acute fatty metamorphosis of the liver. *Am J Obstet Gynecol* 127:400–404, 1977
40. Cano RI, Delman MR, Pitchumoni CS, Lev R, Rosenthal WS: Acute fatty liver of pregnancy. Complicated by intravascular coagulation. *JAMA* 231:159–161, 1975
41. Ober WB, Lecompte PM: Acute fatty metamorphosis of the liver associated with pregnancy. *Am J Med* 19:743–758, 1955
42. Recant L, Lacy P: Fulminating liver disease in a pregnant woman at term. *Am J Med* 35:231–240, 1963
43. Kahil ME, Fred HL, Brown H, David JS: Acute fatty liver of pregnancy. *Arch Intern Med* 113:63–69, 1964
44. Schiffer MA, Dunn I: Jaundice with hepatorenal failure associated with pregnancy or gynecologic procedures. *Obstet Gynecol* 39:241–246, 1972
45. Morrin PAF, Handa SP, Valberg LS, Bencosme SA, Kipkie GF, Wyllie JC: Acute renal failure in association with fatty liver in pregnancy: Recovery after fourteen days of complete anuria. *Am J Med* 42:844–851, 1967
46. Reye RDK, Morgan G, Baral J: Encephalopathy and fatty degeneration of the viscera: A disease entity in childhood. *Lancet* 2:749–752, 1963
47. Mor J, Susin M, Kahn E, Davm F, Teichberg S, McVicar M: Acute renal failure in Reye syndrome. *J Pediatr* 94:69–72, 1979
48. Finkelstein FO, Kashgarian M, Hayslett JP: Clinical spectrum of postpartum renal failure. *Am J Med* 57:649–654, 1974
49. Larcan A, Rauber G, Laprevote MC, Lambert H, Andre JL: Le syndrome urémo-hémolytique du post-partum. *Nouv Presse Méd* 3:1529–1534, 1974
50. Sun NCJ, Johnson WJ, Sung DTW, Woods JE: Idiopathic postpartum renal failure: Review and case report of a successful renal transplantation. *Mayo Clin Proc* 50:395–401, 1975
51. Vandewalle A, Kanfer A, Kourilsky O: Oliguric thrombotic microangiopathy during the fifth month of pregnancy. *Br Med J* 2:479, 1975
52. Beller FK, Intorp HW, Losse H, Loew H, Moenninghoff W, Schmidt EH, Grundmann E: Malignant nephrosclerosis during pregnancy and in the postpartum period (the uremic hemolytic syndrome). *Am J Obstet Gynecol* 125:633–639, 1976
53. Khanh BT, Bhathena D, Vasquez M, Luke RG: Role of heparin therapy in the outcome of adult hemolytic uremic syndrome. *Nephron* 16:292–301, 1976
54. Strauss RG, Alexander RW: Postpartum hemolytic uremic syndrome. *Obstet Gynecol* 47:169–173, 1976
55. Ball JH, Butkus DE, Briggs WA: Postpartum nephrosclerosis. *Rocky Mountain Med J* 74:200–202, 1977
56. Cochran M, Martin JF, Ross B: Postpartum acute renal failure: possible role for endarterial urokinase. *Br Med J* 2:1257, 1977
57. Gomperts ED, Sessel L, Du Plessis V, Hersch C: Recurrent post-partum haemolytic uraemic syndrome. *Lancet* 1:48, 1978
58. Morel-Maroger L, Kanfer A, Solez K, Sraer JD, Richet G: Prognostic importance of vascular lesions in acute renal failure with microangiopathic hemolytic anemia (hemolytic-uremic syndrome): Clinocopathologic study in 20 adults. *Kidney Int* 15:548–558, 1979
59. Clinicopathological Conference: A case of haemolytic uraemic syndrome. *Br Med J* 2:179–184, 1979
60. Ponticelli C, Imbasciati A, Tarantino G, Graziani G, Redaelli B: Post-partum renal failure with microangiopathic haemolytic anaemia. *Nephron* 9:27–41, 1972
61. Churg J, Koffler D, Paronetto F, Rorat E, Barnett RN: Hemolytic uremic syndrome as a cause of postpartum renal failure. *Am J Obstet Gynecol* 108:253–261, 1970
62. Rosenmann E, Kanter A, Bacani RA, Pirani CL, Pollak VE: Fatal late postpartum intravascular coagulation with acute renal failure. *Am J Med Sci* 257:259–273, 1969
63. May HV Jr, Harbert GM Jr, Thornthon WN: Thrombotic thrombocytopenic purpura associated with pregnancy. *Am J Obstet Gynecol* 126:452–458, 1976
64. Fuchs WE, George JN, Dotin LN, Sears DA: Thrombotic thrombocytopenic purpura: Occurrence 2 years apart during late pregnancy in 2 sisters. *JAMA* 235:2126–2127, 1976
65. Mant MJ, Cauchi MN, Medley G: Thrombotic thrombocytopenic purpura: Report of a case with possible immune etiology. *Blood* 40:416–421, 1972
66. Wengeler H, Holzgreve H, Gokel JM, Holzmann K: Thrombotisch-Thrombozytopenische Purpura (Moschcowitz-Syndrom) in der Schwangerschaft. *Geburtsch U Frauenheilk* 36:953–959, 1976
67. Robson JS, Martin AM, Ruckley VA, MacDonald MK: Irreversible post-partum renal failure. *Quart J Med* 37:423–435, 1968
68. Mery JP, Grünfeld JP, Watchi JM, De Montera H: Insuffisance rénale aiguë avec microangiopathie thrombotique chez l'adulte, in *Actualités Néphrologiques de l'Hôpital Necker*, edited by Hamburger J, Crosnier J, Funck-Brentano JL, Paris, Flammarion, 1967, p. 449

69. HABIB R, COURTECUISSE V, LECLERC F, MATHIEU H, ROYER P: Etude anatomo-pathologique de 35 observations de syndrome hémolytique et urémique de l'enfant. *Arch Franç Péd* 26:391-416, 1969
70. HEPTINSTALL RH: *Pathology of the Kidney* (2nd ed). Boston, Little, Brown and Co, 1974, vol. 2, p. 689
71. TOBON H: Malignant hypertension, uremia and hemolytic anemia in a patient on oral contraceptives. *Obstet Gynecol* 40:681-685, 1972
72. BROWN CB, ROBSON JS, THROMSON D, CLARKSON AR, CAMERON JS, OGG CS: Haemolytic uraemic syndrome in women taking oral contraceptives. *Lancet* 1:1479-1481, 1973
73. EPSTEIN FH, SCULLY RE: Case-records of the Massachusetts General Hospital: Post-partum acute renal failure. *N Engl J Med* 288:93-99, 1973
74. ZACHERLE BJ, RICHARDSON JA: Irreversible renal failure secondary to hypertension induced by oral contraceptives. *Ann Intern Med* 77:83-85, 1972
75. ZECH P, RIFLE G, LINDNER A, SASSARD J, BLANC-BRUNAT N, TRAEGER J: Malignant hypertension with irreversible renal failure due to oral contraceptives. *Br Med J* 4:326-327, 1975
76. PRITCHARD JA, PRITCHARD SA: Blood pressure response to estrogen-progestin oral contraceptive after pregnancy-induced hypertension. *Am J Obstet Gynecol* 129:733-739, 1978
77. BERGSTEIN J, MICHAEL A JR, KJELLSTRAND C, SIMMONS R, NAJARIAN J: Hemolytic-uremic syndrome in adult sisters. *Transplantation* 17:487-490, 1974
78. PAZ RA, ELIJOVICH F, BARCAT JA, SANCHEZ-AVALOS JC: Fatal simultaneous thrombocytopenic purpura in siblings. *Br Med J* 4:727-728, 1969
79. GOLDSTEIN MH, CHURG J, STRAUSS L, GRIBETZ D: Hemolytic-uremic syndrome. *Nephron* 23:263-272, 1979
80. GRØTTUM KA, FLATMARK A, MYHRE E, JANSEN H, TEISBERG P, ØYSTESE B, HUSBY G, HOVIG T: Immunological hereditary nephropathy. *Acta Med Scand Suppl* 197:571, 1975
81. KAPLAN BS, THOMPSON PD: Heparin for the hemolytic uremic syndrome. *N Engl J Med* 294:846, 1976
82. AMOROSI EL, KARPATKIN S: Antiplatelet treatment of thrombotic thrombocytopenic purpura. *Ann Intern Med* 86:102-108, 1977
83. THORSEN CA, ROSSI EC, GREEN D, CARONE FA: The treatment of the hemolytic-uremic syndrome with inhibitors of platelet function. *Am J Med* 66:711-716, 1979
84. BYRNES JJ, KHURANA M: Treatment of thrombotic thrombocytopenic purpura with plasma. *N Engl J Med* 297:1386-1389, 1977
85. PONTICELLI C, MAESTRI O, IMBASCIATI E, BRANCACCIO D, ROSSI E: Late recovery of renal function in a woman with the HUS. *Clin Nephrol* 8:367-370, 1977
86. BONNAR J, REDMAN CWG, DENSON KW: The role of coagulation and fibrinolysis in preeclampsia, in *Hypertension in Pregnancy*, edited by LINDHEIMER MD, KATZ AI, ZUSPAN FP, New York, John Wiley and Sons, 1976, p. 85.
87. MCKAY DG: *Disseminated Intravascular Coagulation. An Intermediary Mechanism of Disease*. New York, Harper and Row, 1965, p. 493
88. KINCAID-SMITH P: The similarity of lesions and underlying mechanism in preeclamptic toxemia and postpartum renal failure: Studies in the acute stage and during follow up, in *Gomerulonephritis. Morphology, Natural History, and Treatment*, Part II, edited by KINCAID-SMITH P, MATHEW TH, BECKER EL, New York, John Wiley and Sons, 1973, p. 1013
89. KLEINKNECHT D, KANFER A, JOSSO F: Intravascular coagulation and heparin therapy in acute renal failure: A reappraisal. *Eur J Clin Biol Res* 17:695-700, 1972
90. WARDLE EN: Intravascular coagulation in experimental acute renal failure: Assessment of radio-fibrinogen technique. *Thrombos Diathes Haemorrh* 29:579-591, 1973
91. PRITCHARD JA, CUNNINGHAM FG, MASON RA: Does coagulation have a causative role in eclampsia? in *Hypertension in Pregnancy*, edited by LINDHEIMER MD, KATZ AI, ZUSPAN FP, New York, John Wiley and Sons, 1976, p. 95.
92. RAIJ L, KEANE WF, MICHAEL AF: Unilateral Shwartzman reaction: Cortical necrosis in one kidney following in vivo perfusion with endotoxin. *Kidney Int* 12:91-95, 1977
93. LINDHEIMER MD, KATZ AI: *Kidney Function and Disease in Pregnancy*. Philadelphia, Lea and Febiger, 1977, p. 131
94. KURTZ GG, MICHAEL UF, MOROSI HJ, VAAMONDE CA: Hemodialysis during pregnancy: Report of a case of glutethimide poisoning complicated by acute renal failure. *Arch Intern Med* 118:30-32, 1966